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(54) Title: POLYMER COMPOSITIONS CONTAINING A MACROCYLIC TRIENE COMPOUND

(57) Abstract: A polymer composition for use in delivering a macrocyclic triene compound to a subject is described. The polymer composition is comprised of a polymer substrate containing as the macrocyclic triene compound a 40-0-hydroxy alkyl rapamycin derivative, where the alkyl group contains between 7-11 carbon atoms. The composition is useful for treating any condition responsive to rapamycin or everolimus, and methods of treatment using the polymer composition are described.

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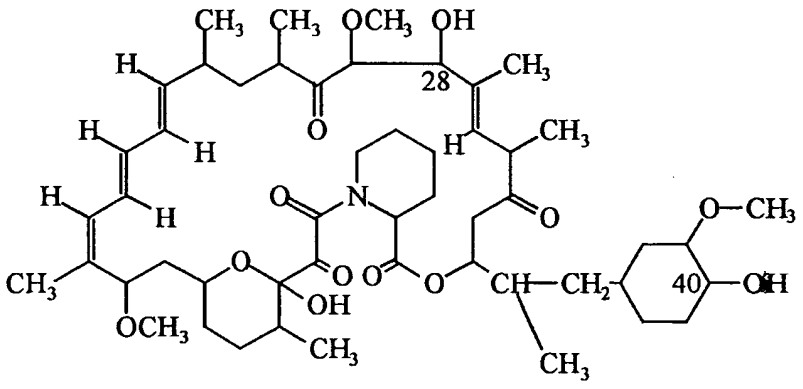
POLYMER COMPOSITIONS CONTAINING A MACROCYCLIC TRIENE COMPOUND

Field of the invention

The present invention relates polymer compositions comprised of a polymer substrate containing a 40-O-hydroxy alkyl substituted rapamycin derivative, where the alkyl has between 7-11 carbon atoms.

Background of the Invention

Rapamycin is a macrocyclic triene compound that was initially extracted from a streptomycete (*Streptomyces hygroscopicus*) isolated from a soil sample from Easter Island (Vezina *et al.*, *J. Antibiot.* 28:721 (1975); U.S. Patent Nos. 3,929,992; 3,993,749). Rapamycin has the structure depicted in Formula I:



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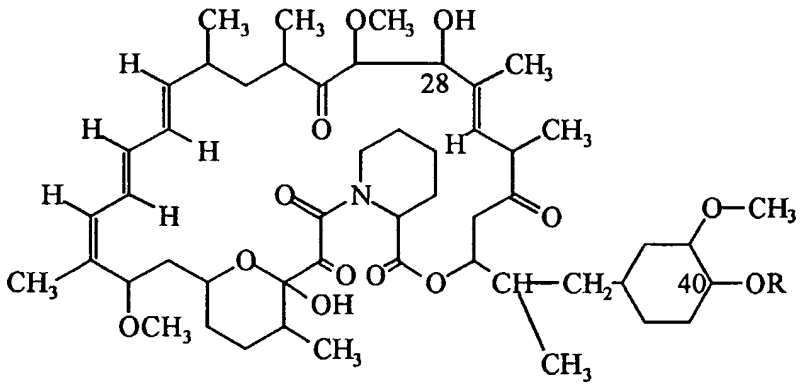
Originally described for use as an antifungal agent (U.S. Patent No. 3, 929,992), it has subsequently found to be an effective agent for other conditions and disorders, including use in the treatment of cancer and tumors (U.S. Patent No. 4,885,171), use for the prevention of experimental immunopathies (experimental allergic encephalitis and adjuvant arthritis; Martel, R., *Can. J. Physiol.*, 55:48 (1977)), inhibition of transplant rejection (U.S. Patent No. 5,100, 899), and inhibition of smooth muscle cell proliferation (Morris, R., *J. Heart Lung Transplant*, 11 (pt. 2) (1992)).

The utility of the compound as a pharmaceutical drug, however, was restricted by its very low and variable bioavailability and its high toxicity. Also, the

rapamycin is only very slightly soluble in water, *i.e.*, 20 micrograms per milliliter, making it difficult to formulate into stable compositions suitable for *in vivo* delivery. To overcome these problems, prodrugs and derivatives of the compound have been synthesized. Water soluble prodrugs prepared by derivatizing rapamycin positions 31 and 40 of the rapamycin structure to form glycinate, propionate and pyrrolidino butyrate prodrugs have been described (U.S. Patent No. 4,650,803). The numerous derivatives of rapamycin described in the art include monoacyl and diacyl derivatives (U.S. Patent No. 4,316,885), acetal derivatives (U.S. Patent No. 5,151,413), silyl ethers (U.S. Patent No. 5,120,842), hydroxyesters (U.S. Patent No. 5,362,718), as well as alkyl, aryl, alkenyl, and alkynyl derivatives (U.S. Patent Nos. 5,665,772; 5,258,389; 6,384,046; WO 97/35575).

Summary of the invention

In one aspect, the invention includes a polymer composition for use in delivering macrocyclic triene compound to an internal target site in a subject. The composition comprises (i) between 20-70 weight percent polymer substrate and (ii) between 30-80 weight percent a macrocyclic triene compound having the structure:



wherein R is CH_2-X-OH, and wherein X is a linear or branched alkyl group containing 6-10 carbon atoms. The composition, when placed against cells at the target site, is effective to achieve a level of uptake of the compound into the target-site cells that is substantially greater than would be achieved by the same polymer substrate containing a rapamycin or everolimus macrocyclic triene

compound.

In one embodiment, the composition is for use in treating a solid tumor, inflammation, or a wound at a target site and is comprised of a suspension of injectable particles that can be localized by injection at the target site.

In another embodiment, polymer substrate in the composition is formed of a bioerodable polymer.

In yet another embodiment, the composition is intended for use in treating a solid tumor, inflammation, or a wound at a target site and takes the form of a patch formed of the polymer substrate and the compound. The drug-containing patch is placed on a surface of a tissue structure, for example, the outer surface of an organ or a tumor, or the outer or inner surfaces of a vessel.

The composition also finds use in treating inflammed tissue or a wound, where the polymer substrate takes the form of a salve for application to the tissue in need of treatment.

The composition also finds use in inhibiting restenosis at a site of injury of a vessel wall, wherein the composition includes a coating carried on a vessel-wall-contacting portion of an expandable vascular stent.

In another embodiment, the composition is intended for use in delivering a macrocyclic triene compound to cells of a mucosal surface. The polymer substrate in the composition has a mucoadhesive surface coating suitable for placement against mucosal tissue.

In any or all of these uses, the compound has, in one embodiment, a structure of the form where R is CH_2-X-OH and X is a linear alkyl group having 6-10 carbon atoms. In another embodiment, R is CH_2-X-OH and X is a linear alkyl group containing 6 carbon atoms.

The polymer substrate, in another embodiment, is comprised of a biodegradable polymer. Exemplary biodegradable polymers include polylactic acids, polyglycolic acid, and copolymers thereof. Suitable polylactic acids include poly(*l*-lactide), poly(*d*-lactide), and poly(*dl*-lactide).

In another embodiment, the macrocyclic triene compound is present at an initial concentration of between 35 and 80 weight percent of the total composition weight.

These and other objects and features of the invention will become more fully apparent when the following detailed description of the invention is read in conjunction with the accompanying drawings.

Brief Description of the Drawings

Fig. 1 is a semi-log plot of relative hydrophobicity (Rm value) as a function of acetone concentration (balance water) for 40-O-hydroxy heptyl (solid circles), everolimus (40-O-hydroxy ethyl rapamycin; open squares), rapamycin (sirolimus; solid diamonds), paclitaxel (open triangles), and dexamethasone (solid squares);

Figs. 2 and 3 illustrate an endovascular stent having a metal-filament body, and formed in accordance with one embodiment of the present invention, showing the stent in its contracted (Fig. 2) and expanded (Fig. 3) conditions;

Fig. 4 is an enlarged cross-sectional view of a coated metal filament in the stent of Fig. 2;

Fig. 5 is an enlarged cross-sectional view of coated, erodable polymer stent;

Figs. 6A and 6B are schematic illustrations of a polymer coating method suitable for use in producing a polymer-coated stent;

Fig. 7 shows a bioerodable polymer stent mounted on a catheter for delivery to a vascular site;

Figs. 8A and 8B is are plots showing release of everolimus from stents carrying a polymer coating;

Fig. 9 is a cross-sectional view of a stent deployed at a vascular site;

Figs. 10A-10C are histological sections of a vessel 28 days after implantation of a bare-metal stent;

Figs. 11A-11C are histological sections of a vessel 28 days after implantation of a metal-filament stent with a polymer coating;

Figs. 12A-12C and 13A-13C are histological sections of a vessel 28 days after implantation of a metal-filament stent with a polymer coating containing everolimus;

Fig 14 is an enlarged histological section of a vessel seen with a filament of the stent employed in Figs. 12A-12C, which has been overgrown by new tissue forming a healed vessel wall;

Fig. 15 is a plot of area of stenosis at 28 days post-implant, as a function of injury score, with a variety of different stents;

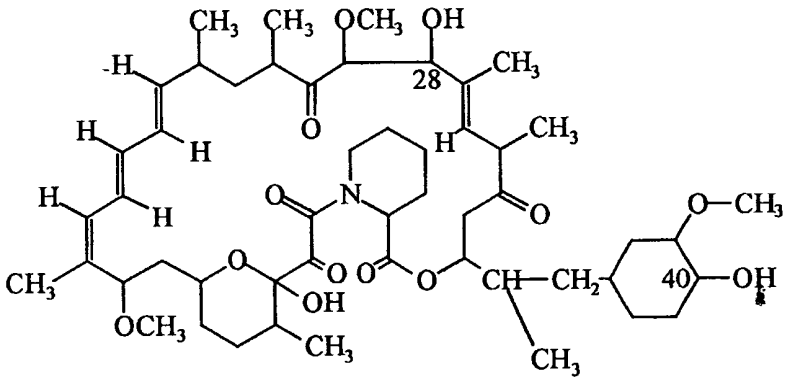
Fig. 16 shows a correlation plot between injury score (Y axis) and B/A (balloon/artery) ratio at time of stent implantation; and

Fig. 17 shows a plot of total amount of drug released, in μg, from a polymer substrate (poly-*dl*- lactic acid) carried on a stent as a function of time, in hours, for everolimus (40-O-hydroxy ethyl rapamycin; solid circles) and for 40-O-hydroxy heptyl rapamycin; (solid squares).

Detailed Description of the Invention

I. Definitions

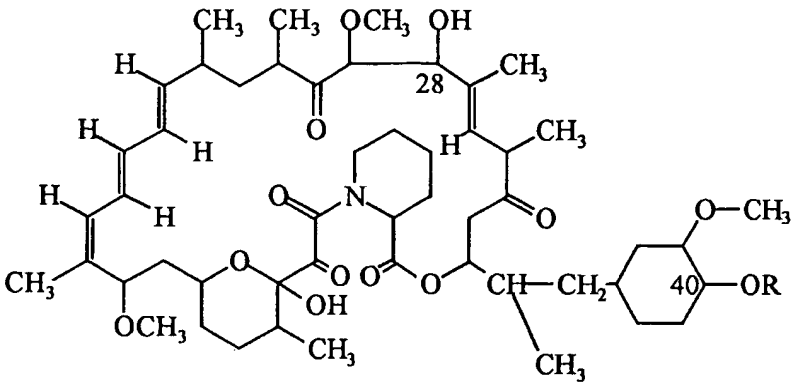
"Rapamycin" as used herein intends a compound of the structure:



This compound is also known in the art as 'sirolimus'.

A "40-O-hydroxy alkyl substituted rapamycin" compound refers to a compound where the hydroxyl group at carbon number 40 in the rapamycin compound is modified to include an hydroxy alkyl. For example, modification at the 40-O position to replace the hydrogen of the hydroxyl group with $(CH_2)_7OH$ is referred to as 40-O-hydroxy heptyl rapamycin.

"Everolimus" intends a compound of the structure:



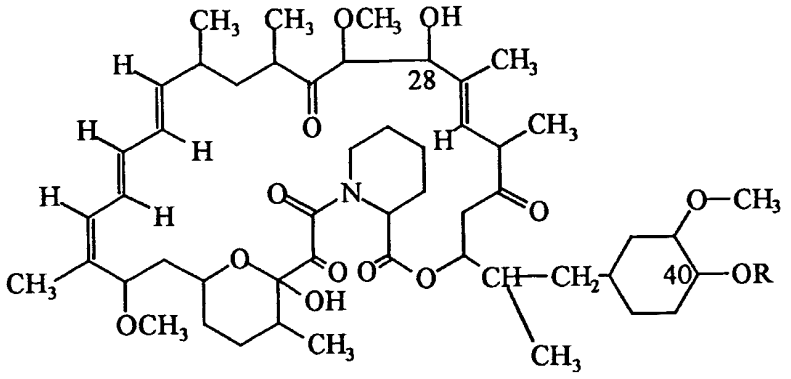
where R is CH_2CH_2OH (hydroxy ethyl).

An "efficacious amount" or an "effective amount" intends a dosage sufficient to provide treatment for the disorder or disease state being treated. This will vary depending on the patient, the disease, and the treatment being effected, but is readily determined using clinical markers particular to the disorder or disease of concern. For example, a cross-sectional area measurement of the amount of new tissue growth inside a stent after implantation and injury of the vessel wall by overexpansion of the stent with a balloon catheter provides a clinical marker for restenosis. A reduction or stabilization of tumor volume after application of a dosage of active drug at a tumor site provides a clinical marker for tumor treatment. A clinical marker relating to organ transplant or vascular graft surgery would be to monitor organ functioning or to monitor continued patency of transplant allografts. For skin wounds, a clinical marker would be to watch for a change in inflammation markers of redness, granuloma formation, or fibrosis. For an enlarged prostate, a clinical marker would be to monitor for any reduction in recurrence of ureter blockage.

II. Polymer Composition

The present invention is directed toward a polymer composition comprising a 40-O-hydroxy alkyl (C7-C11) substituted rapamycin compound. As discussed above, rapamycin and many of its derivatives have low bioavailability, limiting their utility as pharmacologic agents. In the present invention, certain 40-O-hydroxy alkyl derivatives of rapamycin when formulated into a polymer structure have been found to offer improved bioavailability when placed in contact with a

tissue for treatment. The rapamycin compounds for use in the polymer composition are those where the 40-O position is modified as follows:



wherein R is CH_2-X-OH, X is a linear or branched alkyl group containing 6-10 carbon atoms. In one embodiment, X is a linear or branched alkyl having 6-10 carbon atoms or, in another embodiment, 7-11 carbon atoms. In a preferred embodiment, X is a linear alkyl having 6 carbon atoms. Compounds where R is CH_2-X-OH and X is a 6, 7, 8, 9, or 10 carbon alkyl are referred to herein as 40-O-hydroxy heptyl, 40-O-hydroxy octyl, 40-O-hydroxy nonyl, 40-O-hydroxy decyl, and 40-O-hydroxy undecyl, respectively.

Fig. 1 is a semi-log plot showing the relative hydrophobicity (Rm value) of several drugs. Rm values are used as a measure of hydrophobicity (Biagi G., *et al., J. Medicinal Chem.*, 18(9):873 (1975); Ichihaski, T. *et al., Pharm. Res.*, 11(4):508 (1994)). Rm values were determined using the general method of Biagi *et al.* using a reversed-phase thin-layer chromatography technique. This method allows the partitioning of test compounds between a polar mobile phase and a non-polar stationary phase. Measurement of the relative mobility of each compound allows Rm determination. Reverse-phase chromatography was done using HPTLC-RP18F unibond octadecyl modified silica thin-layer chromatography plates (Alltech 63077). The mobile polar phase consisted of water in various concentrations with acetone (v/v). Visualization was by UV quenching at 254 nm. The results are shown in Fig. 1 for the following compounds: 40-O-hydroxy heptyl rapamycin (solid circles), everolimus (40-O-hydroxy ethyl rapamycin; open squares), rapamycin (solid diamonds), paclitaxel (open triangles), and

dexamethasone (solid squares). The y-intercept values for each compound are shown in Table 1.

Table 1

Compound	Y-Intercept[1]
40-O-hydroxy heptyl rapamycin	4.667
40-O-hydroxy ethyl rapamycin (everolimus)	3.966
rapamycin	3.860
paclitaxel	2.659
dexamethasone	2.341

[1]Determined from a liner regression analysis of the data in Fig. 1.

The y-interept values are log, and therefore 40-O-hydroxy heptyl rapamycin is approximately 7 times more hydrophobic than 40-O-hydroxy ethyl rapamycin (everolimus), which is approximately 1 time more hydrophobic than rapamycin. Based on this data, the relative water solubilities of the compounds would be in the order:

dexamethasone>>paclitaxel>>>rapamycin>everolimus>>>>>40-O-hydroxy heptyl rapamycin

Relative to 40-O-hydroxy heptyl rapamycin, rapamycin and everolimus are more like one another in their solubility characteristics, and therefore in their bioavailablilty properties, than either rapamycin or everolimus is like 40-O-hydroxy heptyl rapamycin. The poor water solubility of 40-O-hydroxy heptyl rapamycin would generally lead one to believe it to be an undesirable candidate for use as a pharmacological agent, since such sparingly soluble compounds typically have poor bioavailability and are difficult to formulate for administration. However, as will be shown below, this compound and 40-O-hydroxy alkyl derivatives of rapamycin can be formulated for administration for bioavailability at a treatment site.

Accordingly, in one aspect, the invention provides a polymer composition for use in delivering a 40-O-hydroxy alkyl (C7-C11) substituted rapamycin

compound to an internal site in a patient. Typically, the polymer composition is comprised of between 20-70 weight percent of a selected polymer and between 30-80 weight percent of the 40-O-hydroxy alkyl substituted rapamycin compound. Alternatively, the composition can contain between 30-70 weight percent of a selected polymer and between 30-70 weight percent of a 40-O-hydroxy alkyl substituted rapamycin compound.

As mentioned above, a wide variety of polymers and formulations are contemplated and several specific examples will be discussed in more detail below. In general, the polymer composition serves as a sort of drug reservoir which contains and releases the compound after deposition at a target site.

Polymer Particles

An exemplary polymer composition is a formulation of polymer particles that are suitable for placement *in vivo* via injection or via deposition using device, such as a catheter. The polymer particles can be microporous, macroporous, or non-porous and can be formed of a polymer that is capable of retaining the poorly water soluble 40-O-substituted rapamycin compound.

Porous polymer particles have interconnected pores which open to the particle surface for communication between the exterior of the particle and the internal pore spaces. Exemplary particles for formation of such macroporous reservoirs are described, for example, in U.S. Patent No. 5,135,740, incorporated by reference herein. In brief, porous particles are formed, for example, by suspension polymerization in a liquid-liquid system. In general, a solution containing monomers and a polymerization catalyst is formed that is immiscible with water. An inert solvent miscible with the solution but immiscible with water is included in the solution. The solution is then suspended in an aqueous solution, which generally contains additives such as surfactants and dispersants to promote the suspension or emulsion. Once the suspension is established with discrete droplets of the desired size, polymerization is effected, typically by activating the reactants by either increased temperature or irradiation. Once polymerization is complete, the resulting solid particles are recovered from the suspension. The particles are solid, spherical, porous structures, the polymer having formed around the inert liquid, thereby forming the pore network. The inert

solvent, which served as a porogen, or pore-forming agent, occupies the pores of the particles. The porogen is subsequently removed.

The macroporous particles can also be prepared by solvent evaporation, from either a biodegradable or a non-degradable polymer. For the solvent-evaporation process, the desired polymer is dissolved in an organic solvent and the solution is then poured over a layer of sodium chloride crystals of the desired particle size (Mooney, et al., *J. Biomed. Mater. Res.* 37:413-420, (1997)). The solvent is removed, generally by evaporation, and the resulting solid polymer is immersed in water to leach out the sodium chloride, yielding a porous polymer reservoir. Alternatively sodium chloride crystals can be dispersed in the polymer solution by stirring to obtain a uniform dispersion of the sodium chloride crystals. The dispersion is then extruded dropwise into a non-solvent for the polymer while stirring to precipitate the polymer droplets around the sodium chloride crystals. The solid polymer particles are collected by filtration or centrifugation and then immersed in water to leach out the sodium chloride, yielding a porous polymer reservoir. It will be appreciated that alternatives to sodium chloride include any non-toxic water soluble salt or low molecular weight water soluble polymer which can be leached out to produce the desired porosity.

The porous particles can be loaded with one or more drugs by including the compounds in the polymer during particle formation or by loading the particles post-particle formation. Post-particle loading can be done by, for example, dissolving the drug compound in a solvent that acts to solvate the drug but that is a nonsolvent for the polymer and mixing by stirring the particles and the drug solution. The solution of drug is absorbed by the particles to give a free flowing powder. The particles may then be treated for solvent removal, as needed.

Another exemplary polymer particle composition is non-porous particles, such as microcapsule and microparticles having the compound are contained or dispersed therein. Both microcapsules and microparticles are well known in the pharmaceutical and drug delivery industries (see, for example, Baker, R.W., CONTROLLED RELEASE OF BIOLOGICALLY ACTIVE AGENTS, John Wiley & Sons, NY, 1987; Ranade V. and Hollinger, M., DRUG DELIVERY SYSTEMS, CRC Press, 1996). Microcapsules typically refer to a reservoir of active agent surrounded by a polymer membrane shell. A microparticle typically refers to a monolithic system

where the therapeutic agent(s) is dispersed throughout the particle. There are, however, many formulations falling between these two definitions, such as agglomerates of microcapsules, and such formulations would also be suitable for use herein.

Microcapsules and microparticles can be prepared from biodegradable or non-biodegradable polymers. Microcapsules are readily formed by a number of methods, including coacervation, interfacial polymerization, solvent evaporation, and physical encapsulation methods (, Baker, R.W., CONTROLLED RELEASE OF BIOLOGICALLY ACTIVE AGENTS, John Wiley & Sons, NY, 1987). Microparticles are prepared by numerous techniques known in the art, one simple way being to merely grind a polymer film containing dispersed therapeutic agent into a suitable size. Spray drying particulate therapeutic agent from a polymer solution is another approach. Specific procedures for encapsulation of biologically active agents are disclosed in U.S. Patent No. 4,675,189 and U.S. Patent Application No. 20010033868, which are incorporated by reference herein.

Polymers suitable for particle formation are numerous and varied; the general selection criterion being a polymer capable of carrying the 40-O-hydroxy alkyl substituted rapamycin compound. Exemplary polymers include, but are not limited to, poly(*d*, *l*-lactic acid), poly(*l*-lactic acid), poly(*d*-lactic acid), methacrylate polymers, such as polybutyl methacrylate and the like, ethylene vinyl alcohol (EVOH), ε-caprolactone, ethylvinyl hydroxylated acetate (EVA), polyvinyl alcohol (PVA), polyethylene oxides (PEO), polyester amides, and co-polymers thereof and mixtures thereof. These polymers all have a history of safe and low inflammatory use in the systemic circulation. Typically, between 20-70 weight percent of polymer will be combined with between 30-80 weight percent of the 40-O-hydroxy alkyl substituted rapamycin compound to form the polymer composition.

The particles, whether porous or non-porous, may vary widely in size, from about 0.1 micron to about 100 microns in diameter, preferably from about 0.5 microns to about 40 microns. The particles can be administered as neat particles, or can be formulated in a gel, paste, ointment, salve, or viscous liquid for application at the target site.

As exemplified by the polymer particles, the polymer composition of the invention is one capable of being dispensed or placed at the target site, for

contact of the polymer composition with the tissue at the target site. Those of skill in the art will appreciate that polymer particles are merely one example of a composition that achieves contact with the target tissue. Polymers capable of carrying a load of a hydrophobic compound can be formulated into films, patches, pastes, salves, or gels, all of which can be placed or dispensed at the target site. For example, a simple polymer patch prepared from a polymer loaded with the 40-O-hydroxy alkyl substituted rapamycin compound can be placed on the surface of tissue in need of treatment. Such a tissue surface can be a vessel, an organ, a tumor, or an injured or wounded body surface.

Mucoadhesive Polymer Composition

In another embodiment, the polymer composition is comprised of a polymer substrate having mucoadhesive properties, for placement adjacent mucosal tissue. Mucosal sites in the body include the cul-de-sac of the eye, buccal cavity, nose, rectum, vagina, periodontal pocket, intestines and colon. Mucoadhesive delivery systems exhibit adhesion to mucosal tissues for administration of the compound(s) contained within the mucoadhesive polymer.

A variety of polymeric compositions are used in mucosal delivery formulations. Of particular interest for use with the 40-O-hydroxy alkyl substituted rapamycin compounds are mucoadhesives having a combination of hydrophilic and hydrophobic properties. Adhesives which are a combination of pectin, gelatin, and sodium carboxymethyl cellulose in a tacky hydrocarbon polymer, for adhering to the oral mucosa, are exemplary. Other mucoadhesives that have hydrophilic and hydrophobic domains include, for example, copolymers of poly(methyl vinyl ether/maleic anhydride) and gelatin, dispersed in an ointment base, such as mineral oil containing dispersed polyethylene (U.S. Pat. No. 4,948,580). Another hydrophilic/hydrophobic system is described in U.S. Pat. No. 5,413,792 where a paste-like preparation of a polyorganosiloxane and a water soluble polymeric material is disclosed.

In the present invention, a polymer composition comprised of a mucoadhesive polymer substrate and a 40-O-hydroxy alkyl substituted rapamycin compound is contemplated. The mucoadhesive polymer composition is formulated into a delivery system suitable for placement adjacent a mucosal

surface. The compound when placed adjacent the mucosal tissue elutes from the polymer composition into the tissue. The delivery system can take the form of a patch for placement on the surface of tissue to be treated. The tissue can be an organ, a vessel, a tumor or any body surface needing treatment.

Endovascular Stent

Another exemplary polymer composition for use in the invention is a polymer coating carried on an expandable vascular stent. Figs. 2 and 3 are a schematic illustration of an endovascular stent coated with a polymer composition that carries the 40-O-substituted rapamycin compound. In these figures, a stent 20 is shown, in the stent's contracted (Fig. 2) and expanded states (Fig. 3). The stent includes a structural member or body 22 and an outer coating for holding and releasing the compound, as will be described further below with reference to Figs. 3 and 4.

In the embodiment shown in Figs. 2 and 3, the stent body is formed of a plurality of linked tubular members by filaments, such as members 24, 26. Each member is has an expandable zig-zag, sawtooth, or sinusoidal wave structure. The members are linked by axial links, such as links 28, 30 joining the peaks and troughs of adjacent members. As can be appreciated, this construction allows the stent to be expanded from a contracted condition, shown in Fig. 2, to an expanded condition, shown in Fig. 3, with little or no change in the length of the stent. At the same time, the relatively infrequent links between peaks and troughs of adjacent tubular members allows the stent to accommodate bending. This feature may be particularly important when the stent is being delivered to a vascular site in its contracted state, in or on a catheter. The stent has a typical contracted-state diameter (Fig. 2) of between 0.5-2 mm, more preferably 0.71 to 1.65 mm, and a length of between 5-100 mm. In its expanded state, shown in Fig. 3, the stent diameter is at least twice and up to 8-9 times that of the stent in its contracted state. Thus, a stent with a contracted diameter of between 0.7 to 1.5 mm may expand radially to a selected expanded state of between 2-8 mm or more.

Stents having this general stent-body architecture of linked, expandable tubular members are known, for example, as described in PCT Publication No. WO 99/07308, which is commonly owned with the present application, and which

is expressly incorporated by reference herein. Further examples are described in U.S. Patent Nos. 6,190,406, 6,042,606, 5,860,999, 6,129,755, or 5,902,317, which patents are incorporated by reference herein. Alternatively, the structural member in the stent may have a continuous helical ribbon construction, that is, where the stent body is formed of a single continuous ribbon-like coil. The basic requirement of the stent body is that it be expandable, upon deployment at a vascular injury site, and that it is suitable for receiving a drug-containing coating on its outer surface, for delivering drug contained in the coating into the vessel wall (*i.e.* medial, adventitial, and endothelial layers of tissue) lining the vascular target site. Preferably, the body also has a lattice or open structure, allowing endothelial cell wall ingrowth "through" the stent from outside to inside.

The stent filaments are coated with a drug-release coating composed of a polymer matrix and the 40-O-hydroxy alkyl substituted rapamycin compound distributed within the matrix for release from the stent over an at least a several week period, typically 4-8 weeks, and optionally over a 2-3-month period or more.

Fig. 4 shows, in enlarged sectional view, a stent filament 24 having a coating 32 that covers the filament completely on all sides, that is, on top (the filament side forming the outer surface of the stent body) bottom (the filament side forming the interior surface of the stent) and the opposing filament sides. As will be discussed further below, the coating has a thickness typically between 3 and 30 microns, depending on the nature of the polymer matrix material forming the coating and the relative amounts of polymer matrix and active compound. Ideally, the coating is made as thin as possible, *e.g.*, 15 microns or less, to minimize the stent profile in the vessel at the injury site.

The coating should also be relatively uniform in thickness across the upper (outer) surfaces, to promote even distribution of released drug at the target site. Methods for producing a relatively even coating thickness on stent filaments are discussed below.

Also shown in Fig. 4 is a polymer underlayer 34 disposed between the stent filament and the coating. The purpose of the underlayer is to help bond the coating to the stent-body filaments, that is, to help stabilize the coating on the filaments. As will be seen below, this function is particularly valuable where the coating is formed of a polymer substrate containing a high percentage of the

compound, *e.g.* between 35-80 weight percent compound. One exemplary underlayer polymer is parylene used in conjunction with a polymer substrate formed of bioerodable (poly-*dl*–lactide). Other suitable polymer underlayers are ethylene vinyl alcohol (EVOH), paryLAST™, parylene, silicone, TEFLON™ and other fluoropolymers, that may be deposited on the metal stent surfaces by plasma-coating or other coating or deposition processes. The underlayer has a typical thickness between 1-5 microns.

The polymer forming the substrate may be any biocompatible polymer material from which entrapped compound can be released by diffusion and/or released by erosion of the polymer matrix. Two well-known non-erodable polymers for the coating substrate are polymethylmethacrylate and ethylene vinyl alcohol. Methods for preparing these polymers in a form suitable for application to a stent body are described for example, in US 2001/0027340A1 and WO00/145763, incorporated herein by reference. In general, the limit of drug addition to the polymers is about in the range of 20-40 weight percent.

Bioerodable polymers, particularly poly-*dl*-lactide polymer, are also suitable for coating substrate material. In one general embodiment, of the invention, the coating is a bioerodable poly-*dl*-lactide polymer substrate , *i.e.*, poly-*dl*-lactic acid polymer, that may contain up to 80% by dry weight of the active compound distributed within the polymer substrate. More generally, the coating contains 35-80% dry weight active compound and 20-65% percent by dry weight of the polymer. Exemplary coatings include 25-50% dry weight polymer matrix and 50-75 weight percent active compound. The polymer is formulated with the active compound for deposition on the stent filaments as detailed below.

One preferred coating is formed of 25-50 weight percent poly-*dl*-lactide polymer substrate, and 50-75 weight percent macrocyclic triene immunosuppressant compound, having a coating thickness of between 3-15 microns. The underlayer is formed of parylene, and has a thickness between 1-5 microns. This embodiment typically contains an amount of compound equal to about 15 micrograms drug/mm of stent length.

In an exemplary embodiment, the polymer coating is formed of 15-35 weight percent of an erodable or non-erodable polymer substrate, and 65-85 weight percent of a 40-O-hydroxy alkyl substituted rapamycin compound. The polymer

coating thickness is preferably 10-30 microns, and the stent may include a 1-5 micron polymer underlayer, *e.g.*, parylene underlayer. This embodiment typically contains an amount of compound equal to about 15 micrograms drug/mm of stent length.

The coating may additionally include a second bioactive agent effective to for treating the disease or disorder of concern or to treat any anticipated secondary conditions that might arise. For example, if the 40-O-hydroxy alkyl substituted rapamycin is administered for treatment of restenosis, a second compound to minimize blood-related events, such as clotting, that may be stimulated by the original vascular injury, the presence of the stent or to improve vascular healing at the injury site can be included. Exemplary second agents include anti-platelet, fibrinolytic, or thrombolytic agents in soluble crystalline form or NO donors which stimulate endothelial cell healing and control smooth muscle cell growth. Exemplary anti-platelet, fibrinolytic, or thrombolytic agents are heparin, aspirin, hirudin, ticlopidine, eptifibatide, urokinase, streptokinase, tissue plasminogen activator (TPA), or mixtures thereof. If the 40-O-hydroxy alkyl substituted rapamycin is intended for use as an anti-neoplastic agent, a second agent commonly used for chemotherapy of neoplastic diseases can be included. Exemplary second chemotherapeutic agents include paclitaxel, platinum compounds, cytarabine, 5-fluorouracil, teniposide, etoposide, methotrexate, doxorubicin, and the like. The amount of second-agent included in the stent coating will be determined by the period over which the agent will need to provide therapeutic benefit. The second agent may be included in the coating formulation that is applied to the stent-body filaments, according to known methods.

Bioerodable Stent

In another general embodiment, both the stent body and polymer coating are formed of a bioerodable polymer, allowing complete resorption of the stent over time. The stent preferably is an expandable coiled stent having a helical-ribbon filament forming the stent body (not shown). Self-expandable coil stents are described in US 4,990,155 for implantation into blood vessels and are incorporated herein by reference.

A coiled stent, may be formed using a preform with the final expanded diameter of the preform specified to be slightly larger than the internal lumen size of the blood vessel to be treated with the coil (3.5 mm OD ±1 mm would be common for a coronary artery). More generally, the stent may be formed by molding, in its expanded shape, and placed in its contracted state by twisting around the stent's long axis or forcing the stent radially into a contracted condition for delivery to the blood vessel when mounted on the tip of a catheter. The stent has a total thickness preferably between about 100 and 1000 microns, and a total length of between 0.4 and 10 cm. In fact, an important advantage of a bioerodable stent of this type is that relatively long stents, *e.g.*, over 3 cm in length, can be readily delivered and deployed at a vascular injury site.

Methods for forming balloon-expandable stents formed of a knitted, bioerodable polymer filament such as poly-*l*-lactide have been reported (US 6,080,177). A version of the device has also been adapted to release drugs (US 5,733,327).

A preferred polymer material for forming the stent is poly-*l*-or poly-*dl*-lactide (US 6,080,177). As indicated above, the stent body and coating may be formed integrally as a single expandable filament stent having anti-restenosis compound contained throughout. Alternatively, a bioerodable coating may be applied to a preformed bioerodable body, as detailed below. In the latter case, the stent body may be formed of one bioerodable polymer, such as poly-*l*-lactide polymer, and the coating from a second polymer, such as poly-*dl*-lactide polymer. The coating, if applied to a preformed stent, may have substantially the same compositional and thickness characteristics described above.

Fig. 5. shows a cross section of a filament , *e.g.*, helical ribbon, in a bioerodable stent of the type just described, having separately formed body and coating. The figure shows an internal bioerodable stent filament 36 coated on all sides with a bioerodable coating 38. An exemplary coating is formed of poly-*dl*-lactide and contains between 20-40 weight percent 40-O-substituted rapamycin compound, and 60-80 weight percent polymer substrate. In another general embodiment, the coating contains 45-75 weight percent compound, and 25-55 weight percent polymer matrix.

The bioerodable stent has the unique advantage of treating the entire vessel with one device, either in conjunction with pre-dilatation of the vessel with balloon angioplasty if large obstructions are present, or as a prophylactic implant in patients of high risk of developing significant future blockages. Since the stent is fully biodegradable, it does not affect the patient's chances for later uncomplicated surgery on the vessel, as does a "full metal jacket, " *i.e.*, a string of drug eluting stents containing metal substrates.

A secondary agent, such as indicated above, may be incorporated into the coating for release from the coating over a desired time period after implantation. Alternatively, if a secondary agent is used, it may be incorporated into the stent-body filament if the coating applied to the stent body does not cover the interior surfaces of the stent body. The coating methods described below with respect to a metal-filament stent body are also suitable for use in coating a polymer-filament stent body.

Stent coating methods

Referring now more particularly to the drawings, Figs 5A and 5B are schematic illustrations of the stent coating process according to the invention. A polymer solution 40 is made by dissolving a polymer in a compatible solvent. A 40-O-substituted compound, and if desired, a secondary agent, is added to the solution, either as a suspension or in solution using the same solvent or a different solvent. The completed mixture is placed in a pressurizable reservoir 42. Connected to the reservoir is a fluid pressurization pump 44.

The pressurization pump may be any source of pressure capable of urging the solvent mixture to move at a programmed rate through a solution delivery tube 46. The pressure pump 44 is under the control of a microcontroller (not shown), as is well known in the field of precision dispensing systems. For example, such a microcontroller may comprise 4-Axis Dispensing Robot Model numbers I&J500-R and I&J750-R available from I&J Fisnar Inc, of Fair Lawn, NJ, which are controllable through an RS-232C communications interface by a personal computer, or precision dispensing systems such as Automove A-400, from Asymtek, of Carlsbad, Ca. A suitable software program for controlling an RS232C interface may comprise the Fluidmove system, also available from Asymtek Inc,

Carlsbad, Ca.

Attached to reservoir 42, for example, at the bottom of the reservoir, is a solution delivery tube 48 for delivery of the solvent mixture to the surface of the stent. The pressurizable reservoir 42 and delivery tube 48 are mounted to a moveable support (not shown) which is capable of moving the solvent delivery tube in small steps such as 0.2 mm per step, or continuously, along the longitudinal axis of the stent as is illustrated by arrow X1. The moveable support for pressurizable reservoir 42 and delivery tube 46 is also capable of moving the tip (distal end) of the delivery tube closer to the microfilament surface or up away from the microfilament surface in small steps as shown by arrow Y1.

The uncoated stent is gripped by a rotating chuck contacting the inner surface of the stent at least one end. Axial rotation of the stent can be accomplished in small degree steps, such as 0.5 degree per step, to reposition the uppermost surface of the stent structure for coating by the delivery tube by attachment of a stepper motor to the chuck as is well known in the art. If desirable, the stent can be rotated continuously. The method of precisely positioning a low volume fluid delivery device is well known in the field of X-Y-Z solvent dispensing systems and can be incorporated into the present invention.

The action of the fluid pressurizing pump, X1 and Y1 positioning of the fluid delivery tube, and R1 positioning of the stent are typically coordinated by a digital controller and computer software program, such that the precisely required amount of solution is deposited wherever desired on the surfaces of the stent, whereupon the solvent is allowed to escape, leaving a hardened coating of polymer and agent on the stent surfaces. Typically, the viscosity of the solvent mixture is prepared by varying the amount of solvent, and it ranges from 2 centipoise to 2000 centipoise, and typically can be 300 to 700 centipoise. Alternatively, the delivery tube can be held at a fixed position and, in addition to the rotation movement, the stent is moved along its longitudinal direction to accomplish the coating process.

The X-Y-Z positioning table and moveable support may be purchased from I&J Fisnar. The solution delivery tube preferred dimensions are preferably between 18-28 gauge stainless steel hypotubes mounted to a suitable locking connector. Such delivery tubes may be obtained from EFD Inc of East

Providence, RI. See EFD's selection guide for Special Purpose Tips. The preferred tips are reorder #'s 5118-1/4-B through 5121-1/4-B "Burr-free passivated stainless steel tips with ¼" length for fast point-to-point dispensing of particle-filled or thick materials", reorder #'s 51150VAL-B "Oval stainless steel tips apply thick pastes, sealants, and epoxies in flat ribbon deposits", and reorder #'s 5121-TLC-B through 5125-TLC-B "Resists clogging of cyanoacrylates and provides additional deposit control for low viscosity fluids. Crimped and Teflon lined". A disposable pressurizable solution reservoir is also available from EFD, stock number 1000Y5148 through 1000Y 5152F. An alternate tip for use with the invention is a glass micro-capillary with an I.D. of about 0.0005 to 0.002 inch, such as about 0.001 inch, which is available from VWR Catalog No. 15401-560 "Microhematocrit Tubes", 60 mm length, I.D. 0.5-0.6 mm.

The tubes are further drawn under a Bunsen burner to achieve the desired I.D. for precise application of the polymer/drug/solvent mixture. The programmable microcontroller to operate the stepper motor, and XYZ table is available from Asymtek, Inc. It is within the scope of the invention to use more than one of the fluid dispensing tube types working in concert to form the coating, or alternately to use more than one moveable solution reservoir equipped with different tips, or containing different viscosity solutions or different chemical makeup of the multiple solutions in the same process to form the coating. The chuck and stepper motor system may be purchased from Edmund Scientific of Barrington, NJ.

Typically, as described above, the coating is applied directly onto the outside support surface(s) of the stent, and may or may not cover the entire or a portion(s) of the inside surface(s) of the stent depending on how control is applied to the above described coating system of the present invention, as illustrated in Figs. 6A and 6B. The latter figure shows application of a coating material 52 to top and side regions of a filament 50. Alternatively, the coating or coating mixture can also be applied directly onto the inside surface of the stent. A thin delivery tip may penetrate through one or more of the cut out areas (*i.e.* windows) in the wall of the stent structure, and thereby apply the coating mixture directly onto the inside surfaces at desired areas. In this method, it is possible to apply different coating materials having different drug components to outer and inner sides of the

filaments . For example, the coating on the outer filament surfaces could contain a 40-O-substituted rapamycin compound, and the coating of the inner filament surfaces, one of the above secondary agents or another 40-O-substituted rapamycin compound. If the stent has a large enough diameter, a thin "L-shaped" delivery tip can be inserted into the stent open ends along the longitudinal axis of the stent for the purpose of applying coating to the inside surfaces.

The polymer for use in the invention includes, but is not limited to, poly(*d*, *l*-lactic acid), poly(*l*-lactic acid), poly(*d*-lactic acid), ethylene vinyl alcohol (EVOH), ε-caprolactone, ethylvinyl hydroxylated acetate (EVA), polyvinyl alcohol (PVA), polyethylene oxides (PEO), and co-polymers thereof and mixtures thereof, dissolved in chloroform, or acetone, or other suitable solvents. These polymers all have a history of safe and low inflammatory use in the systemic circulation.

A non-polymer coating of the 40-O-substituted rapamycin which has been ionically bound to the metal stent surface can also be used.

Using the coating system as described, it has been discovered that it is feasible to coat all of the top, side, and inside surfaces of the stent. By the careful selection of a suitable ratio of solvent to polymer, the viscosity of the solution can be adjusted such that some of the solution will migrate down the sides of the strut and actually inhabit the bottom surface before solidifying, as shown in Fig. 6B. By controlling the dwell time of the delivery tube close to the edge of the stent, the amount of polymer coating the edges or bottom of the stent can be increased or reduced. In the embodiment illustrated in Fig. 4, an underlayer 34 of pure polymer and solvent is applied to the stent surfaces 24 first using the coating system of the invention and the solvent is allowed to evaporate. Then a second layer of polymer 32 is applied containing the bioactive agent.

As noted above, a secondary agent may be incorporated into the polymer mixture. As an example, heparin in crystalline form may be incorporated into the coating. The heparin crystals are micronized to a particle size of approximately 1-5 microns and added in suspension to the polymer solution. Suitable forms of heparin are those of crystalline form that exhibit bioactivity in mammalian hosts when applied according to the process of the invention, including heparin salts (*i.e.* sodium heparin and low molecular weight forms of heparin and their salts). Upon deployment of the drug delivering stent into the vessel wall, as seen in Fig.

9, the heparin crystals near the surface of the coating of cured polymer begin to dissolve, increasing the porosity of the polymer. As the polymer slowly dissolves, more heparin and bioactive agent are released in a controlled manner

It should be appreciated however, with reference to Fig. 9, that it is not always desirable to coat the inside surfaces of the stent. For example, coating the inside surface of the stent increases the crimped delivery profile of the device, making it less maneuverable in small vessels. And, after implantation in a vessel, the inside surfaces are directly washed by the flow of blood through the stent, causing any drug released on the inside surface to be lost to the systemic circulation. Therefore, in the embodiments shown in Figs. 4 and 5, the bulk of the cured polymer and agent is deployed on the outside circumference of the stent supports, and secondarily on the sides. In a preferred embodiment, only a minimum amount of polymer and agent is applied on the inside surfaces of the stent. If desired, it is also possible to have at least a portion of the inside surfaces of the stent uncoated or exposed.

Further, the coating of Figs. 4 and 5, may be placed onto the stent filament surfaces in a selective manner. The depth of the coated section may correspond to the volume of bioactive coating to be available for presentation to the tissue. It may be advantageous to restrict the coating from certain areas, such as those which could incur high strain levels during stent deployment.

A uniform underlayer may be first placed on the stent surface to promote adhesion of the coating that contains the bioactive agent, and/or to help stabilize the polymer coating on the stent. The primer coat may be applied by using any of the methods as already known in the art, or by the precision dispensing system of the invention. It is also within the scope of the invention to apply a primer coat using a different polymer material, such as parylene (poly(dichloro-para-xylylene)), or any other material which exhibits good adhesion to both the base metal substrate and the coating which contains the bioactive agent. Parylene (poly(dichloro-para-xylylene)) may be deposited via plasma or vapor deposition techniques as is well known in the art (See U.S. 6,299,604). In one embodiment of the present invention, islands or a layer of a coating containing heparin are formed on inside surface(s) of a stent and an anti-proliferation coating containing the drugs of the present invention as described above is formed on outside

surface(s) of the stent.

Where it is desired to form a coating with a high drug/polymer substrate ratio, *e.g.*, where the drug constitutes 40-80 weight percent of the coating on a metal stent substrate, it is advantageous to form an underlayer on the stent filaments to stabilize and firmly attach the coating to the substrate. The underlayer may be further processed, prior to deposition of the coating material, by swelling in a suitable solvent, *e.g.*, acetone, chloroform, xylene, or mixtures thereof. This approach is described in Example 5 for preparing a stent having a high ratio of everolimus to poly-*dl*-lactide.

Here a parylene underlayer is formed on the stent filaments by plasma deposition, and the underlayer then allowed to swell in xylene prior to final deposition of the coating material. The method was effective in producing coating containing 50% drug in one case and 75% drug in another case in a poly-*dl*-lactide polymer substrate, in a coating having a thickness of only 5-10 microns.

It is also within the scope of the present invention to produce a completely bioerodable stent, as noted above, using the coating system of the current invention. This may be accomplished by making a tubular preform in the shape of the stent to be formed, using an open-top "C-shaped" helical channel into which the dispensing system may deposit the polymer. The preform is open at its outside diameter so that the polymer may be deposited into the preform, typically using one pass, but also multiple passes, if necessary, of the dispensing tube; while creating uniform edges of the stent structure where the polymer is constrained by the preform. The preform is soluble in a solvent which does not dissolve the bio-degradable stent thus created. After the polymer has been deposited and solvent of the polymer solution has evaporated, the assembly may be placed in the solvent which dissolves the preform to free the completed stent structure. A typical material for the preform is sucrose, which may be molded into the desired preform shape using standard injection molding techniques. A typical solvent for the preform is water.

III. Methods of Use

The 40-O-hydroxy alkyl substituted rapamycin compounds are intended for use in treating any condition responsive to rapamycin or to everolimus. This

includes any condition associated with wound healing, such as post-surgical procedures involving a vessel or an organ transplant procedure, neoplastic diseases, where, for example, the polymer composition is placed directly at a site of cancer, such as a solid tumor. Inflammation and infection are also conditions treatable the 40-O-hydroxy alkyl substituted rapamycin derivatives. The compounds can also be used for vascular treatment methods, and specifically for restenosis. The compound is formulated into a polymer substrate for application to an internal target site in a subject, and exemplary polymer substrate formulations are described above. The polymer composition of a polymer coating applied on an expandable stent is particularly suited for treatment of restenosis.

With respect to treatment of vascular injuries, the risk and/or extent of restenosis in a patient who has received localized vascular injury, or who is at risk of vascular occlusion can be minimized using a polymer composition comprising a 40-O-hydroxy alkyl substituted rapamycin compound. Typically the vascular injury is produced during an angiographic procedure to open a partially occluded vessel, such as a coronary or peripheral vascular artery. In the angiographic procedure, a balloon catheter is placed at the occlusion site, and a distal-end balloon is inflated and deflated one or more times to force the occluded vessel open. This vessel expansion, particularly involving surface trauma at the vessel wall where plaque may be dislodged, often produces enough localized injury that the vessel responds over time by cell proliferation and reocclusion. Not surprisingly, the occurrence or severity of restenosis is often related to the extent of vessel stretching involved in the angiographic procedure. Particularly where overstretching is 35% or more, restenosis occurs with high frequency and often with substantial severity, *i.e.*, vascular occlusion.

The stent is placed in its contracted state typically at the distal end of a catheter, either within the catheter lumen, or in a contracted state on a distal end balloon. The distal catheter end is then guided to the injury site, or the site of potential occlusion, and released from the catheter, *e.g.*, by using a trip wire to release the stent into the site, if the stent is self-expanding, or by expanding the stent on a balloon by balloon inflation, until the stent contacts the vessel walls, in effect, implanting the stent into the tissue wall at the site.

Fig. 7 shows an embodiment of a completely biodegradable stent with a delivery catheter suitable for implantation of the device in a blood vessel of the cardiovascular system, for example a coronary artery. The drawing shows the stent 53, also referred to as a "drug coil", in a partially released position. The stent, which is a self-expanding coil type, is formed from polylactic acid and contains one or more active biological agents.

The coil is created using a preform, with the final expanded diameter of the preform specified to be slightly larger than the internal lumen size of the vessel to be treated with the coil. After removing the preform, the drug coil is wound down by twisting the ends in opposite directions into a coil of smaller radius and thusly compressed along its entire length down under a slideable sheath to a delivery diameter is approximately 1/3 of its final expanded diameter at body temperature. The drug coil is thin enough in thickness (approximately 25-125 microns) to be readily bent in a tighter radius to form a compressed coil at the Internal diameter of the sheath. The sheath is slideably disposed on a delivery catheter 55 suitable for delivery of the stent in its compressed state to the target vessel. Sheath 54 has a gripping means 56 at its proximal end by which the angioplasty operator may pull back the sheath and fully release the drug coil when the tip of the delivery catheter is in position in the vessel.

The center of the delivery catheter 55 has a lumen of approximately 0.014" diameter, in which a guidewire 57 having a flexible tip 58 may be slideably disposed. The delivery catheter further has a luer hub 59 for connection of the inner lumen to a Y-connector and hemostasis valve, as is well known in the angioplasty art. The OD of the delivery catheter with slideable sheath may be in the range of 2-4 F. (French size), or larger if peripheral arteries are being treated.

Since the drug coil is fully biodegradable, it does not affect the patients' chances for later uncomplicated surgery on the vessel, as a full metal jacket does. While bare metal coils are often placed in vessels to create thromboembolism and complete blockage in certain neurovascular applications, surprisingly it has been determined that the biocompatible polymer, poly (*dl*-lactic) acid (PDLA), and mixtures thereof, in the disclosed configuration provide adequate mechanical strength to support the injured vessel following angioplasty, and further do not create embolism and thus are exemplary materials for manufacture of drug coils of

the present invention,

Once deployed at the site, the stent begins to release active compound into the cells lining the vascular site, to inhibit cellular proliferation. Fig. 8A shows everolimus release kinetics from two stents, each having an approximately 10 micron thick polymer coating (closed squares). Drug-release kinetics were obtained by submerging the stent in a 25% ethanol solution, which greatly accelerates rate of drug release from the stent coating. The graphs indicate the type of drug release kinetics that can be expected in vivo, but over a much longer time scale.

Fig. 8B shows drug release of everolimus from polymer coatings placed on metal stent substrates. The upper set of curves show drug release where the coating has been applied directly to the metal surface. The lower set of curves (showing slower release) were obtained by applying an underlayer or primer coat of parylene to the metal stent surface, followed by coating of the surface. As seen, the primer increases the mechanical adhesion of the coating to the sent surface, resulting in slower breakdown of the bioerodeable coating and slower release of drug. Such a configuration is useful where it desired to have a strongly attached stent coating which can withstand repeated abrasions during tortuous maneuvering of the drug eluting stent inside the guide catheter and/or vessel, and/or where it is desired to slow down the drug release for extended treatment of the atherosclerosis disease process at the implant site following implantation of the device.

Fig. 9 shows in cross-section, a vascular region 60 having an implanted stent 62 whose coated filaments, such as filament 64 with coating 66, are seen in cross section. The figure illustrates the release of active compound from each filament region into the surrounding vascular wall region. Over time, the smooth muscle cells forming the vascular wall begin to grow into and through the lattice or helical openings in the stent, ultimately forming a continuous inner cell layer that engulfs the stent on both sides. If the stent implantation has been successful, the extent of late vascular occlusion at the site will be less than 50%, that is, the cross-sectional diameter of flow channel remaining inside the vessel will be at least 50% of expanded stent diameter at time of implant.

Trials in a swine restenosis animal model as generally described by Schwartz *et al.* ("Restenosis After Balloon Angioplasty-A Practical Proliferative Model in Porcine Coronary Arteries", Circulation 82:(6) 2190-2200, Dec 1990.) demonstrate the ability of the stent of this invention to limit the extent of restenosis, and the advantages of the stent over currently proposed and tested stents, particularly in cases of severe vascular injury, *i.e.*, greater than 35% vessel stretching. The studies are summarized in Example 4.

Briefly, the studies compare the extent of restenosis at 28 days following stent implantation, in bare metal stents, polymer-coated stents, and polymer coated stents containing high or low concentrations of sirolimus (rapamycin) and everolimus.

Table 1 in Example 4 shows that both rapamycin (Rapa-high or Rapa-low) and everolimus stents (C-high or C-low) greatly reduced levels of restenosis, with the smallest amount of restenosis being observed in the high-dose everolimus stent. Similar results were obtained in studies on animals with low injury (Table 2).

Figs. 10A-10C are examples of stent cross-sections of neointimal formation at 28 days in a bare metal S-Stent (available from Biosensors International Inc, Newport Beach, CA). Figs. 11A-11C are examples of neointimal formation in a polymer-coated (no drug) S-Stent; and Figs. 12A-12C and 13A-13C of neointimal formation in everolimus/polymer coated stents. In general, the vessels with everolimus-coated stent treatment appeared to be well-healed with a well established endothelial layer, evidence of complete healing and vessel homeostasis at 28 days. Fig. 14 is an example of vessel cross-section at 91X magnification showing healing and establishment of an endothelial layer on the inside of the vessel lumen at 28 days post implant.

The photographs indicate that the most favorable combination for elimination of restenosis at 28 days is the C-high, or C-Ulight formulation (see Example 4) , which contained 325 microgram and 275 microgram dosages of everolimus, respectively, on a 18.7 mm length stent. The data predicts a 50% reduction in restenosis compared to a currently marketed bare metal stent (the S-Stent) at 28 days follow-up in outbred juvenile swine. The data also shows that the drug everolimus is better than, or at least equivalent to the 180 microgram

dosage of sirolimus on the same stent/polymer delivery platform. These results are supported by morphometric analysis (Example 4).

Fig. 15 shows "best fit" linear regression curves of the chosen dosings of agents in polymers, coated on the S-Stent, relating injury score to area stenosis at follow-up. Area Stenosis is an accurate indicator of neointimal formation which is determined by morphometric analysis. As can be seen from this chart, the high everolimus stent was the only coating in the group of samples tested that exhibited a negative slope vs. increasing injury score. This analysis suggests that the C-high coating may be capable of controlling restenosis in an injured coronary artery which is virtually independent of injury score. None of the other coating formulations tried exhibited this unique characteristic.

Fig. 16 shows the relationship between balloon overstretch of the vessel, as measured by balloon/artery ratio (B/A Ratio), and vessel injury, in the animal experiment. This data shows that use of an over-expanded angioplasty balloon to create a high controlled vessel injury is a reasonably accurate method of creating a predictable and known vascular injury in the porcine model.

Fig. 17 shows the elution profile of everolimus (solid circles) and 40-O-hydroxy heptyl rapamycin (solid squares) from a polymer coating of poly (*dl*-lactic acid) carried on a stent. Elution of the compounds from the polymer into ethanol/water (25/75 ratio) was measured as a function of time. Release of 40-O-hydroxy heptyl rapamycin at the 8 hour time point was approximately 1.7 times greater than that of everolimus. At later times, the release of 40-O-hydroxy heptyl rapamycin was approximately 1.5 times greater than the release of everolimus. Accordingly, the invention contemplates a polymer composition comprised of a polymer substrate and a 40-O-hydroxy alkyl substituted rapamycin compound which releases the compound into ethanol/water at room temperature at rate that is at least about 1.5 times greater than the release of everolimus from the polymer substrate.

From the foregoing, it can be seen how various objects and features of the invention are met. A polymer structure containing a 40-O-hydroxy alkyl substituted rapamycin compound having a Rm value substantially greater than the Rm value of everolimus or of rapamycin is contemplated for use in a composition for administration to a target treatment site. When placed adjacent tissue in need

of treatment, the 40-O-hydroxy alkyl substituted rapamycin compound elutes from the polymer substrate to the tissue. The composition is suitable for treatment of any condition that is responsive to treatment with rapamycin or everolimus, including neoplastic diseases, conditions involving inflammation, infections, wound healing, transplant rejection, and restenosis. Conditions contemplated for treatment include those where the polymer composition can be locally deposited or placed at the site in need of treatment, such as a wound, a tumor, or a site of restenosis, inflammation, or infection.

EXAMPLES

The following examples illustrate various aspects of the making and using the stent invention herein. They are not intended to limit the scope of the invention.

Example 1

Preparation of Everolimus and derivatives thereof

STEP A. Synthesis of 2-(t-butyldimethylsilyl)oxyethanol(TBS glycol).

154 ml of dry THF and 1.88g NaH are stirred under in a nitrogen atmosphere in a 500 mL round bottom flask condenser. 4.4 mL dry ethylene glycol are added into the flask, resulting in a large precipitate after 45 minutes of stirring. 11.8 g tert-butyldimethylsilyl chloride is added to the flask and vigorous stirring is continued for 45 minutes. The resulting mixture is poured into 950 mL ethylether. The ether is washed with 420 mL brine and solution is dried with sodium sulfate. The product is concentrated by evaporation of the ether in vacuo and purified by flash chromatography using a 27x5.75 cm column charged with silica gel using a hexanes/Et_2O (75:25v/v) solvent system. The product is stored at 0° C.

STEP B. Synthesis of 2-(t-butyldimethylsilyl)oxyethyl triflate (TBS glycol Trif).

4.22 g TBS glycol and 5.2 g 2,6-lutidine are combined in a double-necked 100 mL flask with condenser under nitrogen with vigorous stirring. 10.74 g of trifluoromethane sulfonic anhydride is added slowly to the flask over a period of 35-45 minutes to yield a yellowish-brown solution. The reaction is then quenched

by adding 1 mL of brine, and the solution washed 5 times in 100 mL brine to a final pH value of between 6-7. The solution is dried using sodium sulfate, and concentrated by evaporation of the methylene chloride in vacuo. The product is purified using a flash chromatography column of approximately 24x3 cm packed with silica gel using hexane/Et_2O (85:15 v/v) solvent system, then stored at 0° C.

STEP C. Synthesis of 40-O-[2-(t-butyldimethylsilyl)oxy]ethyl-rapamycin (TBS Rap).

400 mg rapamycin, 10 mL of toluene, and 1.9 mL 2,6-lutidine are combined and stirred in a 50 mL flask maintained at 55-57 °C. In a separate 3 mL septum vial, 940 µL 2,6-lutidine is added to 1 mL toluene, followed by addition of 2.47 g TBS glycol Trif. The contents of the vial are added to the 50 mL flask and the reaction allowed to proceed for 1.5 hours with stirring. 480 µL 2,6-lutidine plus an additional 1.236 g TBS glycol Trif is added to the reaction flask. Stirring is continued for an additional hour. Finally, a second portion of 480 µL 2,6-lutidine and 1.236 g TBS glycol Trif is added to the mixture, and the mixture is allowed to stir for an additional 1-1.5 hours. The resulting brown solution is poured through a porous glass filter-using vacuum. The crystal like precipitate is washed with toluene until all color has been removed. The filtrate is then washed with 60 mL saturated $NaHCO_3$ solution twice and then washed again with brine. The resulting solution is dried with sodium sulfate and concentrated in vacuo. A small quantity of a hexane/EtOAc (40:60 v/v) solvent is used to dissolve the product, and purification is achieved using a 33x2 cm flash chromatography column packed with silica gel, and developed with the same solvent. The solvent is removed in vacuo and the product stored at 5 °C.

STEP D. Synthesis process of 40-0-(2-hydroxyl)ethyl-rapamycin (everolimus).

A pyrex glass dish (150x75 mm) is filled with ice and placed on a stirring plate. A small amount of water is added to provide an ice slurry. 60-65 mg of TBS-Rap is first dissolved in a glass vial by adding 8 mL methanol. 0.8 mL 1N HCl is added to the vial, the solution is stirred for 45 minutes and then neutralized by adding 3 mL aqueous saturated $NaHCO_3$. 5 mL brine is added to

the solution, followed with 20 mL EtoAc, resulting in the formation of two phases. After mixing of the phases, a separatory funnel is used to draw off the aqueous layer. The remaining solvent is washed with brine to a final pH of 6-7, and dried with sodium sulfate. The sodium sulfate is removed using a porous glass filter, and the solvent removed in vacuo. The resulting concentrate is dissolved in EtoAc/methanol (97:3) and then purified using in a 23 x 2 cm flash chromatography column packed with silica gel, and developed using the same solvent system. The solvent is removed in vacuo and the product stored at 5° C.

Example 2

Preparation of stent containing everolimus in a poly-*dl*-lactide coating

100 mg poly (*dl*-lactide) was dissolved into 2 mL acetone at room temperature. 5 mg everolimus was placed in a vial and 400 µL lactide solution added. A microprocessor-controlled syringe pump was used to precision dispense 10 µL of the drug containing lactide solution to the stent strut top surfaces. Evaporation of the solvent resulted in a uniform, drug containing single polymer layer on the stent.

A 15 µL volume was used in a similar manner to coat the stent top and side strut surfaces, resulting in a single layer coating on the stent strut top and sides.

Example 3

In vitro drug release from stent containing everolimus in a poly-*dl*-lactide coating

In vitro drug release was conducted by placing the coated stents into 2 mL pH 7.4 phosphate buffered saline solution containing 25% ETOH, and preserved with 0.05% (w/v) sodium azide and maintained at 37 °C. Sampling was periodically conducted by withdrawing the total buffer volume for drug measurement while replacing solution with a similar volume of fresh buffer (infinite sink). Fig. 8 illustrates drug release from two similar stents coated with a single polymer layer microdispensed in this manner.

Example 4

Animal Implant Tests

A. QCA Results of safety and dose-finding studies in swine

A challenging treatment condition for the drug eluting stent is a severely injured vessel, since the degree of restenosis (neointimal formation) increases directly with extent of vessel injury. Experiments were conducted in pigs, and a substantial number of the vessels which were the target of drug-coated stent implants were seriously injured (averaging approximately 36% overstretch injury of the vessel) using an angioplasty balloon. This caused severe tearing and stretching of the vessel's intimal and medial layers, resulting in exuberant restenosis at 28 days post implant. In this way, it was possible to assess the relative effectiveness of various dosings of drug and of drug to polymer weight ratios on the same metal stent/polymer platform for reduction of restenosis at 28 days post-implant.

Test Platform Abbreviations:

"Bare stent" refers to an 18.7 mm bare metal stent of a corrugated ring design (*i.e.* a currently marketed "S-Stent" as manufactured by Biosensors Intl., Inc).

"C-high" refers to an 18.7 mm long stent carrying 325 micrograms of everolimus in a PDLA (poly-*dl*-lactic acid) polymer coating.

"C-low" refers to an 18.7mm long stent carrying 180 micrograms of everolimus in a PDLA polymer coating.

"Rapamycin-high" refers to an 18.7 mm long stent carrying 325 micrograms of sirolimus in a PDLA polymer coating.

"Rapamycin-low" refers to an 18.7 mm long stent carrying 180 micrograms of sirolimus in a PDLA polymer coating.

"C-Ulight" refers to an 18.7 mm long stent carrying 275 micrograms of everolimus in an ultrathin coating of PDLA polymer (37% drug to polymer weight ratio).

"C-Ulow" refers to an 18.7 mm long stent carrying 180 micrograms of

everolimus or equivalent in an ultrathin coating of PDLA polymer (37% drug to polymer weight ratio).

"Polymer stent" refers to an 18.7 mm S-Stent stent covered by PDLA polymer coating only.

"B/A" is the final inflated balloon-to-artery ratio, an indication of the extent of overstretching of the vessel.

"Mean Lumen Loss (MLL)" is determined from an average of three measurements taken inside the stent internal lumen at time of implant minus the average of three measurements at follow-up angiography, and indicates the amount of neointima that has formed inside the stent.

Methods:

Drug-eluting stents using a metal wire-mesh scaffold of a corrugated ring design (*i.e.* S-Stent) and polymer coating were implanted in out-bred juvenile swine (alternately Yucatan Minipigs for implant studies lasting longer than 28 days), using different dosings of either the drug everolimus or the drug sirolimus. At the time of implant, Quantitative Coronary Angiography (QCA) was performed to measure the diameter of the vessels both before and after stent implantation. At 28 days, or longer when specified in the table below, the animals were again subjected to QCA in the area of the stent, prior to euthanization.

Following euthanasia of animals according to approved protocols, the hearts were removed from the animals and pressurized formaldehyde solution was infused into the coronary arteries. The coronary segments containing the stents were then surgically removed from the surface of the heart and subsequently fixed in acrylic plastic blocks for transverse sectioning with a diamond saw. 50 micron thick sections of the acrylic material containing cross-sections of the vessels located proximally, center, and distally were then optically polished and mounted to microscope slides.

A microscope containing a digital camera was used to generate high resolution images of the vessel cross-sections which had been mounted to slides. The images were subjected to histomorphometric analysis by the procedure as follows:

A computerized imaging system Image Pro Plus 4.0 through an A.G. Heinze slide microscope for a PC-based system was used for histomorphometric measurements of:

1. The mean cross sectional area and lumen thickness (area circumscribed by the intima/neointimal-luminal border); neointimal (area between the lumen and the internal elastic lamina, IEL, and when the IEL was missing, the area between the lumen and the remnants of media or the external elastic lamina, EEL); media (area between the IEL and EEL); vessel size (area circumscribed by the EEL but excluding the adventitial area); and adventitia area (area between the periadventitial tissues, adipose tissue and myocardium, and EEL).

2. The injury score. To quantify the degree of vascular injury, a score based on the amount and length of tear of the different wall structures was used. The degree of injury was calculated as follows:

0 = intact IEL

1 = ruptured IEL with exposure to superficial medial layers (minor injury)

2 = ruptured IEL with exposure to deeper medial layers (medial dissection)

3 = ruptured EEL with exposure to the adventitia.

The following table shows the results of the QCA analysis (measurements of mean late loss due to restenosis) at follow-up QCA. The data in the tables below under column heading "neo-intimal area" report the results of morphometic analysis of stents and vessels removed from the pigs at follow-up (f/u):

Table 1: Results of "high injury" experiment

Device Description	B/A Ratio (avg)	Days to follow-up	Mean Lumen Loss (mm)	Neo-Intima Area (mm^2)	Stent numbers
Bare Metal Stent	1.33	28	1.69	5.89	31,39,40,45,47,50
Polymer Coated	1.36	28	2.10	5.82	32,41,43,48,51,60
Rapamycin-high	1.39	28	1.07	3.75	42,44,49,65,69,73
Rapamycin-low	1.42	28	0.99	2.80	52,56,61,64,68,72
C-high	1.37	28	0.84	3.54	54,55,59,63
C-low	1.36	28	1.54	3.41	53,57,58,62,66,70, 74
C-Uhigh	1.36	28	0.85	2.97	67,75,92,103

B. Low-injury studies

To further determine which dosage of everolimus would be best in a lightly injured vessel, more typical of the patient with uncomplicated coronary disease and a single denovo lesion, the everolimus-eluting stents were implanted to create moderate to low overstretch injury (approximately 15%). Farm swine were used for a 30 day experiment, and adult Yucatan minipigs were implanted for a 3 month safety study. The angiographic results were as follows:

Table 2: QCA Results of "low injury" experiments

Device Description	B/A ratio	Days post implant	Mean Lumen Loss (mm)	Neo-Intima Area (mm^2)	Stent numbers
Bare Metal Stent	1.14	28	0.95	2.89	20,22,26,29
Bare Metal Stent	1.13	90			76,80,84,87,91
C-Uhigh	1.15	28	0.60	2.14	94,96,98,102
C-Ulow	1.09	28	0.49	2.26	93,95,97,100,101
C-Uhigh	1.15	90			77,81,85,86,90

The above data predict that with either the C-Ulow or C-Uhigh doses of everolimus will produce a 45-48% reduction in neointimal formation in a low to moderately injured vessel.

C. Morphometric analysis

The total cross-sectional area inside each stent, and cross-sectional area of new tissue (neo-intima) that had formed inside the stent were measured by computer, and the percent area stenosis computed. The average vessel injury score, neo-intimal area, and percent area stenosis for each formulation of drug and polymer, averaging three slices per stent, is shown in the table below.

Table 3: Results of "high injury" experiment

Device Description	Injury Score	Days to follow-up	Neo-Intimal Area (mm^2)	Area Stenosis (%)	Stent numbers
Bare Metal Stent	1.9	28	5.89	0.72	31,39,40,45,47,50
Polymer Coated	2.11	28	5.82	0.70	32,41,43,48,51,60
Rapamycin-high	2.10	28	3.75	0.55	42,44,49,65,69,73
Rapamycin-low	1.90	28	2.80	0.43	52,56,61,64,68,72
C-high	1.89	28	3.54	0.38	54,55,59,63
C-low	2.1	28	3.41	0.53	53,57,58,62,66,70,74
C-Uhigh	2.13	28	2.97	0.45	67,75,92,103

Morphometric analysis is considered a highly accurate method of measuring in-stent restenosis in the pig coronary model. In the high injury model, the C-High formulation produced the lowest amounts of neointima formation in the "high injury" experiment at 28 days; however, the C-Uhigh had the highest injury score of the group, and still managed a very low percent area stenosis of 0.45. Therefore, the data independently confirm the findings of the QCA analysis, and supports the choice of C-Uhigh as the preferred formulation for human trials.

D. Histological analysis

The slides for the C-Uhigh and sirolimus-Low were submitted to an experienced cardiac pathologist, who reviewed the vessel cross-sections for evidence of inflammation, fibrin, and endothelialization of the newly healed vessel lumen. No difference was found between the histological changes caused by the sirolimus and everolimus eluting stents. In general, the vessels appeared to be well-healed with a well established endothelial layer, evidence of complete

healing and vessel homeostasis at 28 days. Fig. 14 is an example of vessel cross-section at 91X magnification showing healing and establishment of an endothelial layer on the inside of the vessel lumen at 28 days post-implant.

E. Comparison to published results

Carter *et al.* have published results of sirolimus-coated stents using a Palmaz-Schatz metal stent in swine. A table comparing the published results of Carter to the experimental results using the polymer-coated stent herein is shown below:

Table 4

DEVICE DESCRIPTION	Vessel Overstretch (%)	Mean Late Loss (mm)	Std Deviation (mm)	Neointima Cross-Sectional Area (mm^2)
S-Stent BARE METAL control	33.5% ± 9.2%	1.80	±0.5	7.6
S-Stent Polymer-Only Coated	34.9% ± 4.8%	2.02	±0.8	8.5
S-Stent Polymer/Rapamycin 325 micrograms	32.9% ± 10.1%	0.66	±0.2	3.27 (-57% vs control)
S-Stent Polymer/everolimus 325 microGrams	36.8% ± 8.5%	0.74	±0.3	3.61 (-50% vs control)
PS Stent BARE* control	10-20%	1.19	---	4.5
PS Stent Polymer-only	10-20%	1.38	---	5.0
PS Rapamycin-eluting Stent* 166 microGrams	10-20%	0.70	---	2.9 (-35.5% vs control)
PS Rapamycin-eluting Stent* 166 micrograms (Slow Release)	10-20%	0.67	---	2.8 (-37.7% vs control)
PS Rapamycin-eluting Stent* 450 micrograms	10-20%	0.75	---	3.1 (-31.1% vs control)

Example 5

Preparation of stent with high drug loading

As-marketed metal corrugated-ring stents ("S-stent, corrugated ring design, Biosensors Intl), 14.6mm in length, were coated with an approximately 2 micron thick layer of parylene 'C' primer coating using a plasma deposition process. Parylene coated stents were placed in xylene overnight at ambient temperature. A stock poly(*d,l*)-lactic acid (PDLA) solution containing 50 μg/μl PDLA was prepared by dissolving 100 mg PDLA in 2 mL acetone.

To prepare stents containing a drug to polymer ratio of 50%, 5 mg everolimus was dissolved in 100 μL of the PDLA stock solution. An additional 20 μL acetone was added to aid in dispensing the solution. The stents were removed from the xylene and carefully blotted to remove solvent. A total of 5.1 μL coating solution was dispensed onto the outer surface of each stent. The stents were dried at ambient temperature and placed into overnight desiccation. This resulted in a total of 212 μg everolimus contained in 212 μg PDLA per stent.

To prepare stents containing a drug to polymer ratio of 75%, 5 mg everolimus and 33.3 μL stock PDLA solution were mixed. An additional 33.3 μL acetone was added and the mixture was dissolved. Stents were removed from the xylene and blotted similar to above. A total of 2.8 μL coating solution was dispensed onto the outer surface of each stent. The stents were dried at ambient temperature and placed into overnight desiccation. This resulted in a total of 212 μg everolimus contained in 70 μg PDLA per stent.

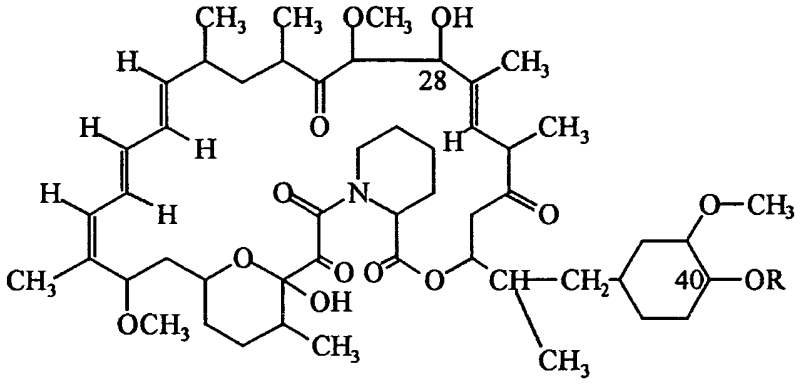
The finished stents exhibited an approximately 5 microns-thick coating of everolimus/PDLA , or slightly milky appearance, which was smoothly distributed on the top and side surfaces, and firmly attached to the metal strut surfaces.

IT IS CLAIMED:

1. A polymer composition for use in delivering macrocyclic triene compound to an internal target site in a subject, comprising

(i) between 20-70 weight percent polymer substrate and

(ii) between 30-80 weight percent a macrocyclic triene compound of the form:



wherein R is CH_2-X-OH, and wherein X is a linear or branched alkyl group containing 6-10 carbon atoms; said composition when placed against cells at the target site, being effective to achieve a level of uptake of the compound into the target-site cells that is substantially greater than would be achieved by the same said polymer substrate containing a rapamycin or everolimus macrocyclic triene compound.

2. The composition according to claim 1, for use in treating a solid tumor, inflammation, or a wound at a target site wherein the composition includes a suspension of injectable particles that can be localized by injection at the target site.

3. The composition according to claim 2, wherein the polymer substrate in the composition is formed of a bioerodable polymer.

4. The composition according to claim 1, for use in treating a solid tumor, inflammation, or a wound at a target site wherein said polymer substrate is a patch for placement on an outer surface of a tissue structure.

5. The composition according to claim 1, for use in treating inflammed tissue or a wound, wherein said polymer substrate takes the form of a salve for application to the tissue in need of treatment.

6. The composition according to claim 1, for use in inhibiting restenosis at a site of injury of a vessel wall, wherein said composition includes a coating carried on a vessel-wall-contacting portion of an expandable vascular stent.

7. The composition according to claim 1, for use in delivering a macrocyclic triene compound to cells of a mucosal surface, wherein said polymer substrate has a mucoadhesive surface coating. .

8. The composition according to any one of claims 1-8 wherein R is CH_2-X-OH and X is a linear alkyl group having 6-10 carbon atoms.

9. The composition according to any one of claims 1-8 wherein is R is CH_2-X-OH and X is a linear alkyl group containing 6 carbon atoms.

10. The composition according to claim 1, wherein said polymer substrate is a comprised of a biodegradable polymer.

11. The composition according to claim 10, wherein said biodegradable polymer is selected from the group consisting of polylactic acids, polyglycolic acid, and copolymers thereof.

12. The composition according to claim 11, wherein said polylactic acid is selected from the group consisting of poly(*l*-lactide), poly(*d*-lactide), and poly(*dl*-lactide).

13. The composition according to claim 12, wherein said compound is present at an initial concentration of between 35 and 80 weight percent of said composition.

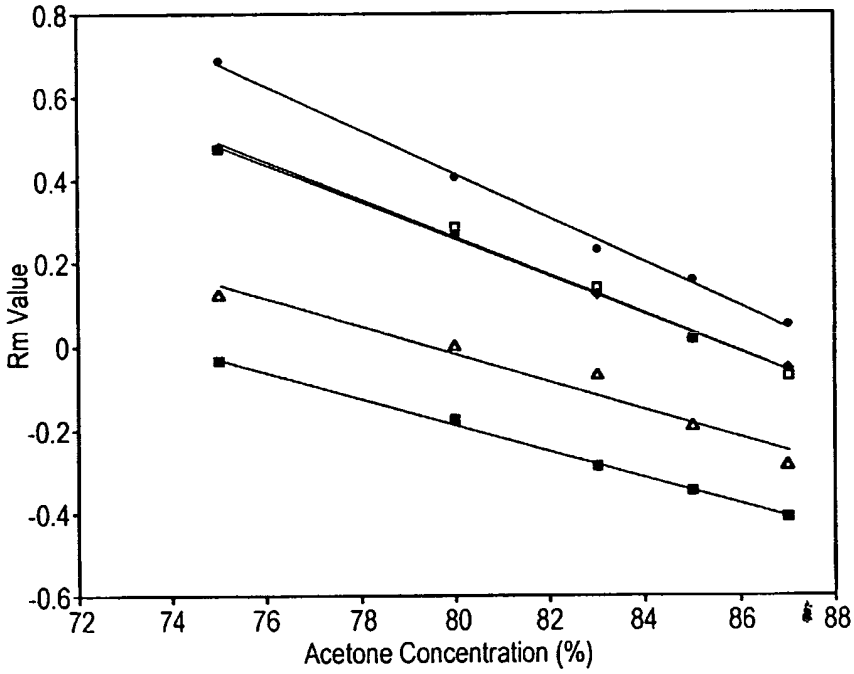

0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
Rm Value
72
74
76
78
80
82
84
86
88
Acetone Concentration (%)

Fig. 1

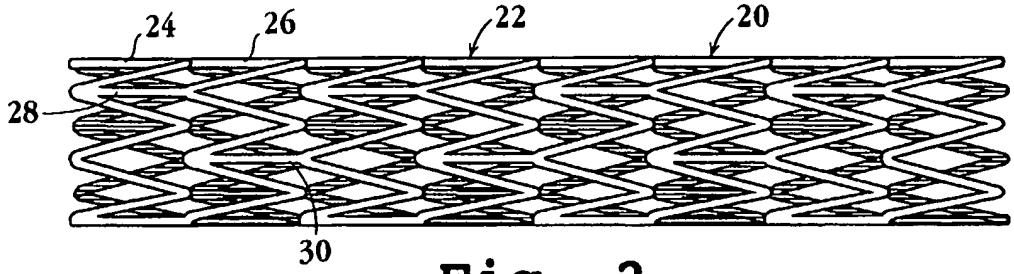


Fig. 2

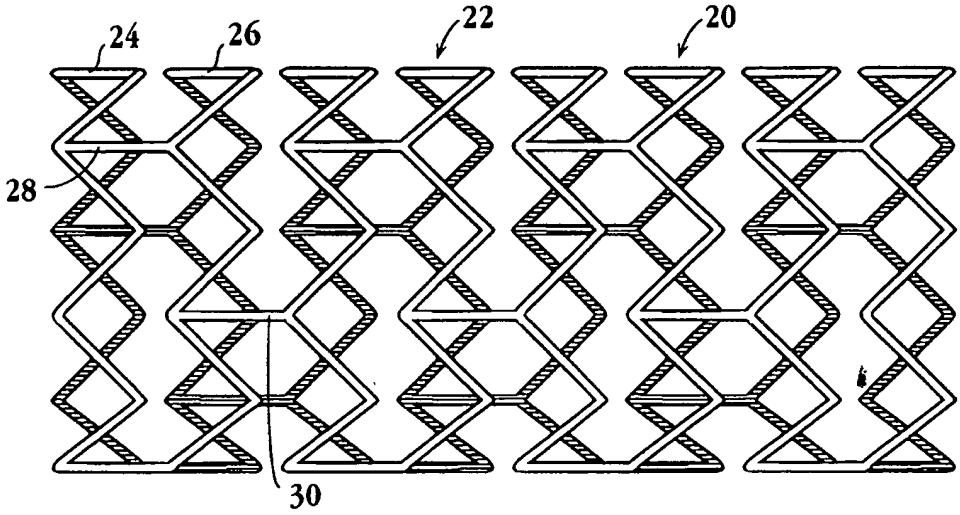


Fig. 3

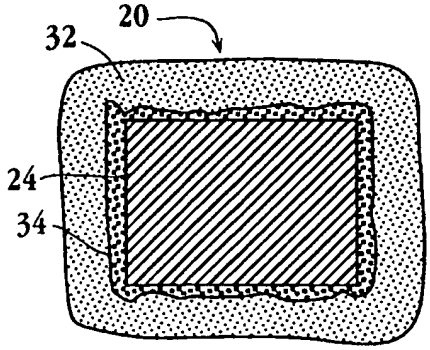


Fig. 4

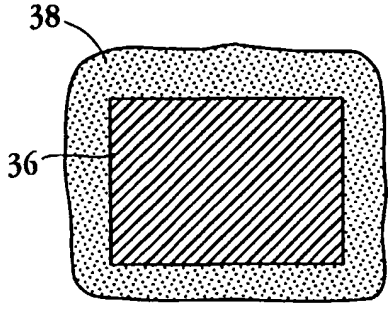


Fig. 5

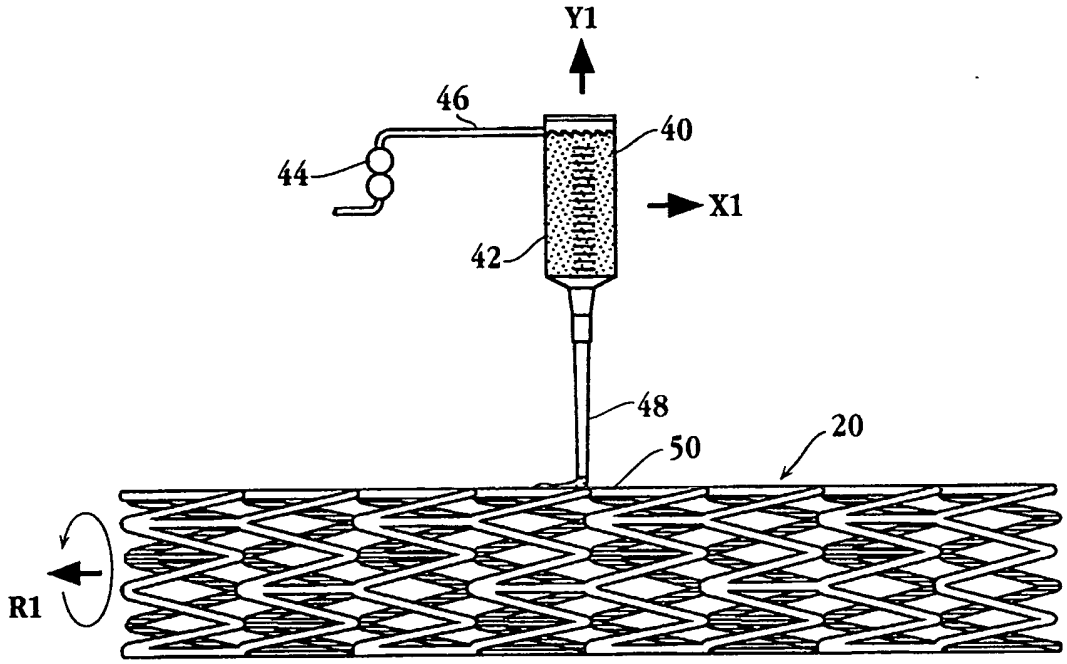


Fig. 6A

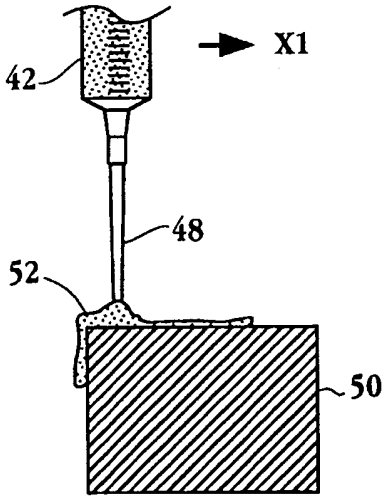


Fig. 6B

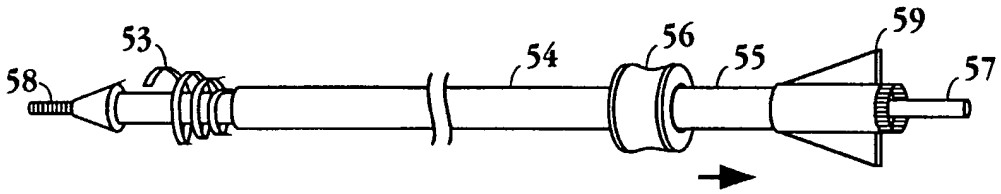


Fig. 7

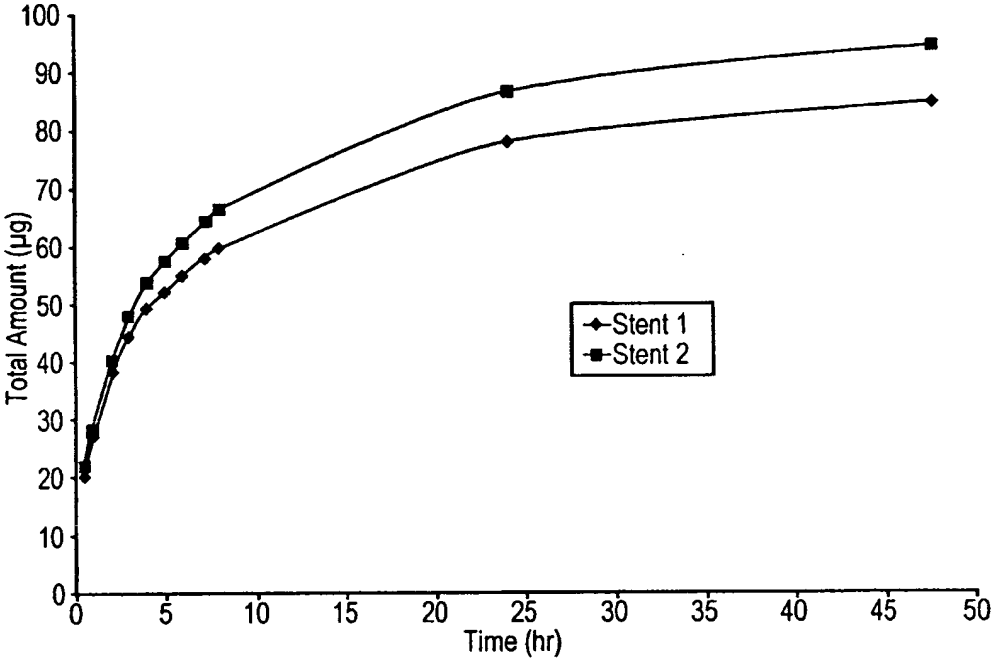

Total Amount (µg)
Time (hr)
Stent 1
Stent 2

Fig. 8A

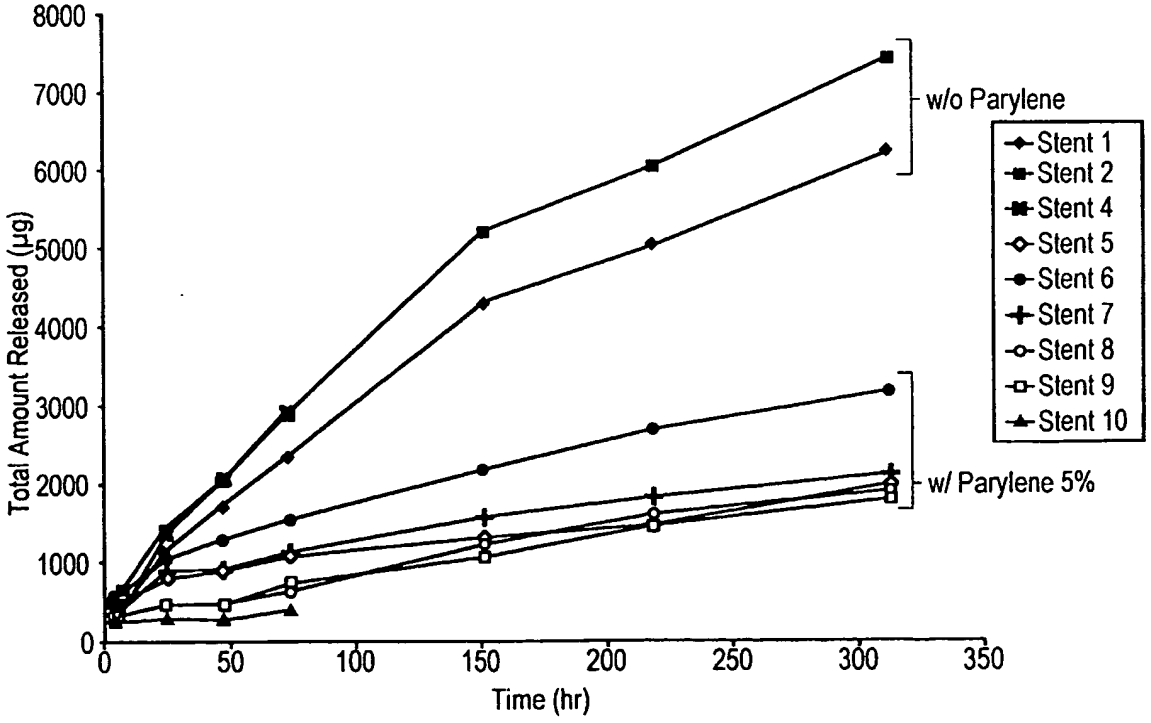

Total Amount Released (µg)
Time (hr)
w/o Parylene
w/ Parylene 5%
Stent 1
Stent 2
Stent 4
Stent 5
Stent 6
Stent 7
Stent 8
Stent 9
Stent 10

Fig. 8B

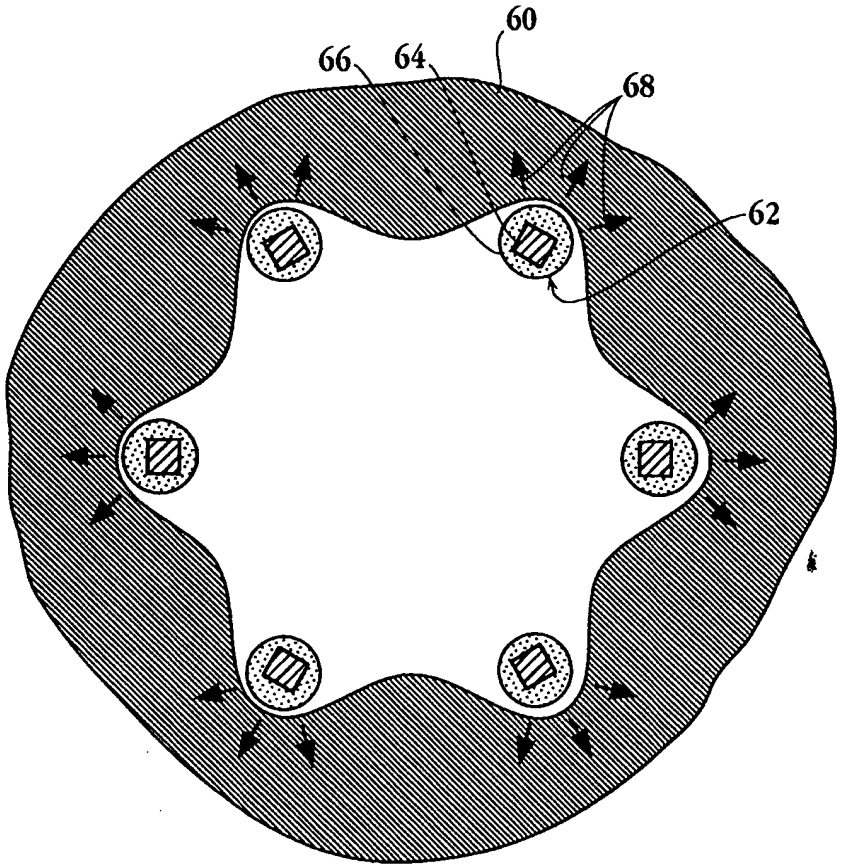


Fig. 9

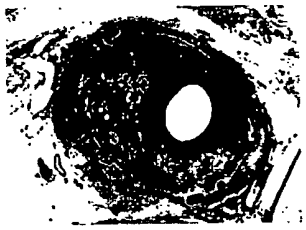


Fig. 10A

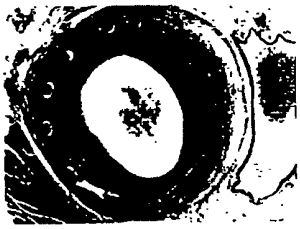


Fig. 11A

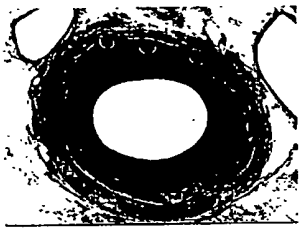


Fig. 10B

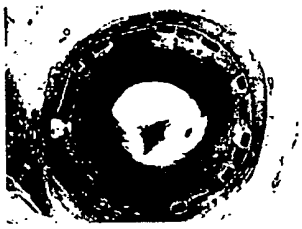


Fig. 11B

Fig. 10C

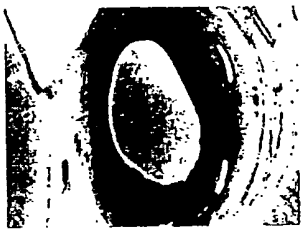


Fig. 11C

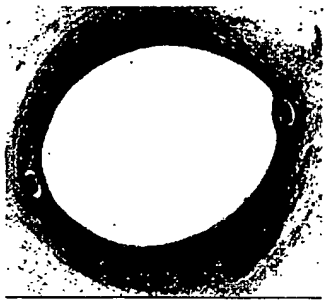


Fig. 12A

Fig. 13A

Fig. 12B

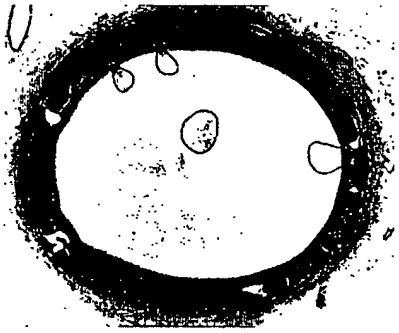


Fig. 13B

Fig. 12C

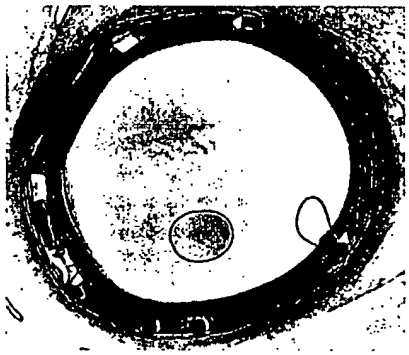


Fig. 13C

Fig. 14

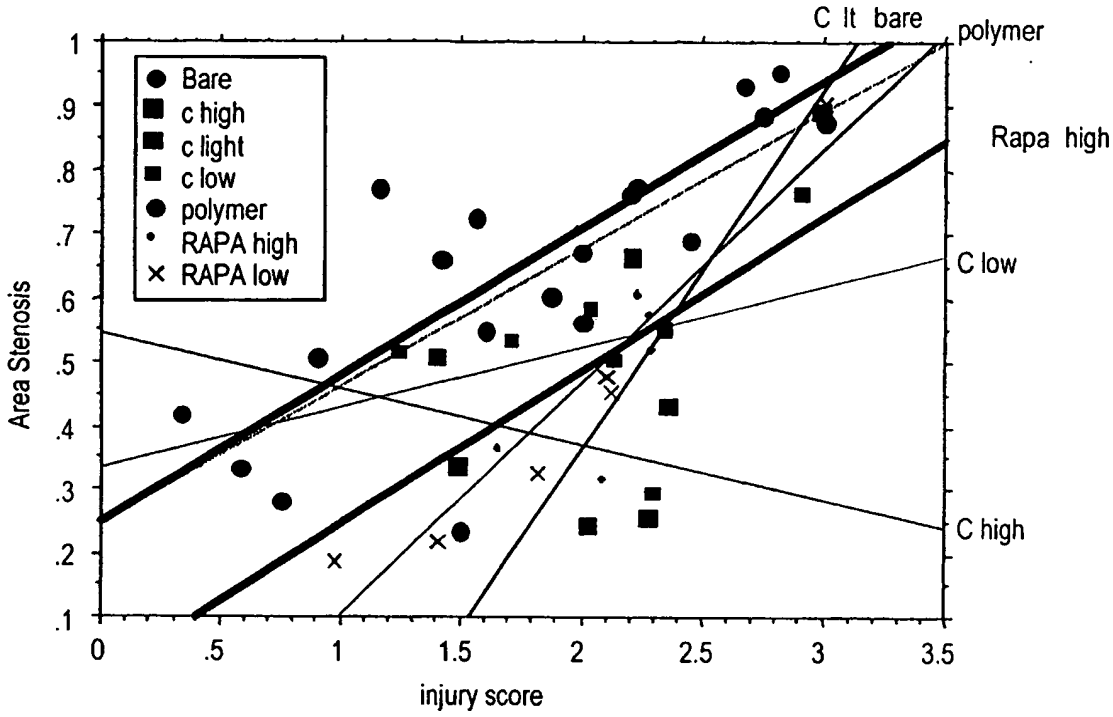

C lt bare
polymer
Rapa high
C low
C high
Bare
c high
c light
c low
polymer
RAPA high
RAPA low
Area Stenosis
injury score
1
.9
.8
.7
.6
.5
.4
.3
.2
.1
0
.5
1
1.5
2
2.5
3
3.5

Fig. 15

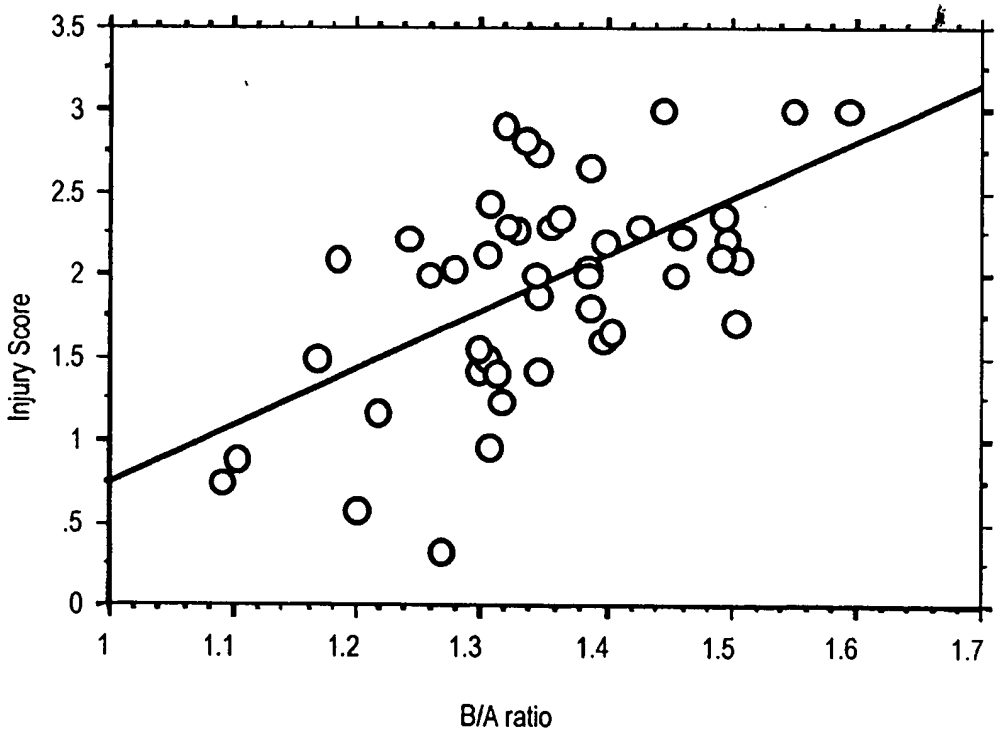

Injury Score
B/A ratio
3.5
3
2.5
2
1.5
1
.5
0
1
1.1
1.2
1.3
1.4
1.5
1.6
1.7

Fig. 16

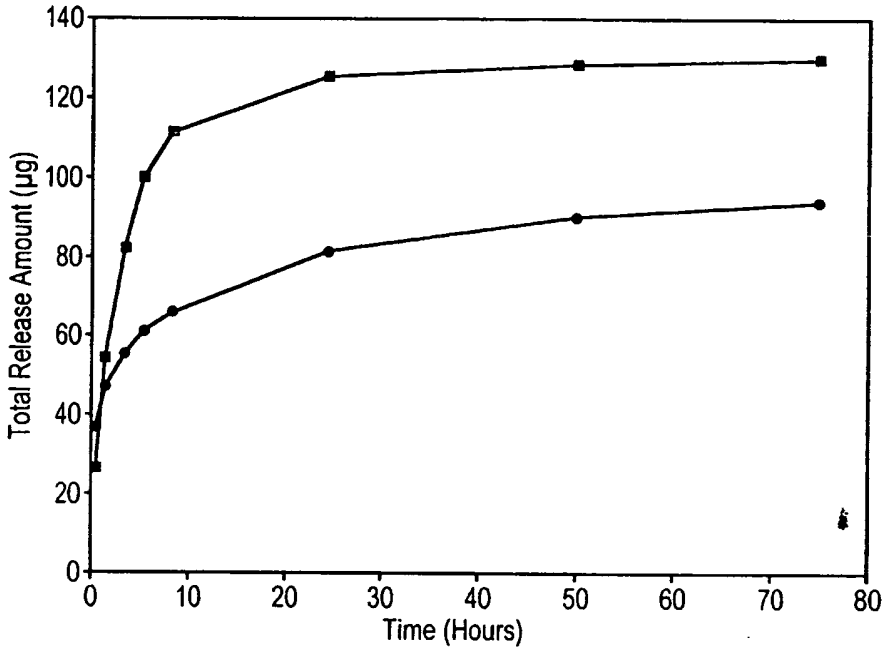

Total Release Amount (µg)
140
120
100
80
60
40
20
0
0
10
20
30
40
50
60
70
80
Time (Hours)

Fig. 17